Remarks

Claims 1-15, 29, 30 and 32-52 are pending in the application upon entry of the herein amendment. Claims 1-15, 29, 40, 41, 45 and 46 have been withdrawn from consideration pursuant to a restriction requirement. Claim 31 is cancelled by the herein amendment. Claims 30, 32-39, 42-44 and 47-52 stand rejected. Reconsideration is requested in view of the above changes and the following remarks.

Sequence Listing

A substitute sequence listing is submitted herewith, to correct the error in SEQ ID NO:3 noted in the report accompanying the June 23, 2009 office action. A Statement Under 37 C.F.R. 1.825 appears at the foot of this document.

Specification

The specification paragraph at page 51, lines 11-25, has been amended to delete the hyperlink.

Priority

The Detailed Action asserts that the claims under examination are not entitled to the priority of GB 0327499 and GB 0327493. As the priority claim is irrelevant to the competence of the asserted prior art, it is respectfully submitted that it was not necessary for Examiner to make a determination of priority entitlement. In any event, applicants do not acquiesce in the finding, and reserve the right to contest the same, in the event that entitlement to the priority of the British applications becomes a relevant consideration to any further prior art rejections that may be raised.

Response to 35 USC 102 Rejection

Claims 30, 34-39, 49 and 50 have been rejected as being anticipated by Iwase *et al.*, as the Examiner alleges that Iwase teaches a c-FLIP inhibitor and a chemotherapeutic agent, and that the culture medium can be regarded as a pharmaceutical composition.

The Examiner notes that Iwase et al teaches the chemotherapeutic agents cisplatin (CDDP) and 5-FU inhibit the expression of c-FLIP. Claim 30 has been amended to specify that

the c-FLIP inhibitor is an antisense or RNAi agent. Iwase describes the treatment of OSCC cell lines with combinations of c-FLIP antisense, CDDP, or 5-FU, and the Fas antibody CH-11. Results relating to a combination of chemotherapeutic agent and c-FLIP antisense are shown in Iwase Figure 6D. As can be seen from that figure, the only combination for which a significant increase in Fas- mediated apoptosis was shown (compared to untreated cells) was for the combination of c-FLIP antisense oligonucleotides, CDDP and 5-FU, and CH-11. No significant difference was shown for either of the combinations of c-FLIP antisense oligomer nucleotides, CH-11 and either CDDP or 5-FU. The significant effect on apoptosis demonstrated by Iwase therefore only relates to combinations comprising both CDDP and 5-FU as well as c-FLIP antisense and CH-11.

Amended claim 30 recites, in part, a pharmaceutical composition consisting of a c-FLIP inhibitor which is an antisense or RNAi agent, and a chemotherapeutic agent which is a thymidylate synthase inhibitor or a topoisomerase I inhibitor.

In view of the "consists of" language used in claim 30, the claimed pharmaceutical composition is novel over the teaching of Iwase et al, which only discusses FLIP-antisense, 5-FU and anti-FAS MAb. Where the chemotherapeutic agent of the claim 30 composition is a topoisomerase I inhibitor, the composition optionally further contains a death receptor binding member. As neither CDDP nor 5-FU is a topoisomerase 1 inhibitor, claim 30 is not anticipated by Iwase.

As claim 30 is not anticipated by Iwase et al, each of claims 34-39, which depend on claim 30, are likewise not anticipated.

Furthermore, the pharmaceutical composition of claim 30 is also not obvious in view of Iwase et al. The present inventors have demonstrated the supra-additive effect of c-FLIP inhibition and a topoisomerase I inhibitor, CPT-11, on treatment of cancer cells. This supra-additive effect could not have been predicted at the time the invention was made from Iwase's combination treatment of c-FLIP antisense with the platinum cytotoxic agent CDDP. Accordingly the portion of the subject matter of claim 30 directed to the combination f a c-FLIP inhibitor and a topoisomerase I inhibitor would not have been obvious in view of Iwase et al.

Similarly, the remaining portion of the subject matter of claim 30 — provision of a c-FLIP inhibitor together with a thymidylate synthase inhibitor in the absence of a death receptor binding member — is clearly not obvious over Iwase, as Iwase provides no suggestion of a significant anti-cancer effect in the absence of Fas agonists such as CH-11.

The present application demonstrates a supra-additive effect of c-FLIP inhibition with thymidylate synthase inhibitors in the absence of death receptor binding members and thus enables the use of such a treatment regime for the treatment of cancer.

Moreover, the teaching of Iwase that only a combination of c-FLIP antisense, CDDP, 5-FU and the death receptor binding member CH-11 increases apoptosis in OSCC cells, would lead the skilled artisan away from considering the supra-additive effects observed when using only two of the four components.

As such, amended claim 30, and dependent claims 32-39, would not have been obvious over the Iwase et al., or any other cited prior art.

For the same reasons, claims 49 and 50, are neither anticipated nor rendered obvious over Iwase. These claims are directed to pharmaceutical compositions comprising (a) a c-FLIP inhibitor, wherein said c-FLIP inhibitor is an antisense or RNAi agent, and (b) a thymidylate synthase inhibitor or a topoisomerase I inhibitor, wherein the composition does *not contain a death receptor binding member, or a nucleic acid encoding said binding member*. Iwase requires an anti-FAS MAb, which is a form of death receptor binding member, and therefore teaches away from any composition where such a binding member is absent.

Response to 35 USC 103 Rejections

Claims 30, 31, 34, 36-39, 42, 47 and 49-52 have been rejected under 35 USC 103 as being allegedly unpatentable over Siegmund *et al.* in view of Xiang *et al.* and Wajant *et al.*, (US 20040126791). Claim 31 has been cancelled.

The Examiner alleges that that Wajant et al. teaches dsRNAs against c-FLIP and an apoptosis inducing drug such as TRAIL for chemotherapy. However, from a review of Wajant et al. it appears that paragraph [0064] generally describes a combination of a dsRNA that targets RNAs (primary or processed) of target cFLIP genes and "other means of treatment such as

surgery, chemotherapy, or radiation therapy". However, in paragraph [0009] it is taught that "[...] radiation and chemotherapy have significant side effects, and are generally avoided if possible". In view of this discrepancy in teachings, it would appear that the combination of dsRNAs against c-FLIP and a chemotherapeutic agent is merely speculative, at best. In contrast to the speculative comment in Wajant that TRAIL could be used in combination with chemotherapy, or with surgery or radiation therapy, the present inventors have clearly identified specific combinations of active agents which provide for supra-additive effects. The generic disclosure provided by Wajant cannot be considered to provide any suggestion of these specific combinations.

While Examiner has argued that it would have been obvious to one of skill in the art to combine the siRNA treatment of Siegmund with the CPT-11 of Xiang in order to form a composition for the treatment of tumors; it is clear from Wajant et al, which was filed after the publication of these two documents, that the authors of this document, despite a number being in common with those of Siegmund, did not suggest such a combination.

Moreover, based on the teaching in the abstract of Siegmund that "chemotherapy can have a broad range of unwanted side effects", and based on the teaching on page 731 that "even trimeric soluble TRAIL may exert cytotoxic effects on normal tissue when combined treatment with chemotherapeutic drugs is required", the skilled artisan would not be motivated to combine TRAIL with other chemotherapeutic agents.

Indeed as Siegmund teaches that therapies involving TRAIL and chemotherapy are associated with side effect problems, which can be circumvented through the use of TRAIL and c-FLIP therapies instead of chemotherapy, the skilled artisan would be led away from providing TRAIL and chemotherapy in a combined treatment.

According, the composition and kits of claims 30, 42. 49 and 51, and their dependent claims, would not have been obvious over the asserted combination of references, at the time the invention was made.

Without prejudice to the foregoing, applicants point to the following further bases of distinction of certain of the claims subject to rejection.

Although each of the cited documents utilizes TRAIL in the composition they disclose, there is no teaching that binding members to FAS (claim 32), and in particular the FAS antibody CH-11 (claim 33), would have the same effect as TRAIL. Thus, these claims further distinguish over the asserted combination of references.

As to claims 49-52, the Examiner alleges at pages 6 and 14 of the office action that it would have been obvious to formulate the composition or kit as claimed such that it does not include a death receptor binding member. However, this runs contrary to the basis provided by the Examiner as the motivation for combining the teachings of Siegmund et al. and Xiang et al., *i.e.*, that TRAIL, a death receptor binding member, is the shared component of the compositions provided by Siegmund et al. and Xiang et al. Based on this common teaching of TRAIL, it would not have been obvious from the asserted combination of references to develop a pharmaceutical composition for the treatment of a cancer which does not include TRAIL. Accordingly, the compositions and kits of claims 49-52, which do not include a death receptor binding member, would clearly not have been obvious in view of the asserted combination of references.

While the Examiner has indicated at page 14 that one of ordinary skill in the art, aware of Siegmund et al. and Xiang et al, ***could*** make compositions comprising one or more of these three agents (c-FLIP siRNA, TRAIL and a chemotherapeutic agent) for use in treating cancer, there is no reference teaching cited by the Examiner evidencing that one ***would*** make such compositions, or event that one would be motivated to try to make such combinations. Indeed, there is no expectation that the claimed combinations would be useful. It is only with the benefit of hindsight and applicants' disclosure that the combinations are made.

Moreover, the demonstration by the inventors that synergistic effects in the killing of tumor cells can be obtained in the absence of TRAIL is unexpected.

Reconsideration and withdrawal of the Section 103 rejection of claims 30, 34, 36-39, 42, 47 and 49-52 over the combination of Siegmund *et al.*, Xiang *et al.* and Wajant *et al.* is respectfully requested.

Claims 43, 44 and 48 have been rejected as being unpatentable over Siegmund *et al.* in view of Xiang *et al,*. Wajant *et al.*, Tuschl et al (1) and Tuschl et al (2).

At page 15 of the office action, the Examiner refuted applicants' previously filed arguments that RNAi agents comprising SEQ ID NOs 1 or 2 are not obvious, by arguing that the assertion by the applicant that SEQ ID NOs 1 and 2 were extremely potent when compared to other siRNA molecules was unsupported. The present application clearly teaches at page 60 lines 29 to 32, pages 62 and 63, that a concentration of FTsiRNA (SEQ ID NO 1) as low as 1nm results in activation of caspase 8. Further, pages 69 and 70 discuss nanomolar concentrations of FTsiRNA (SEQ ID NO 1) which lead to increased apoptosis.

The concentrations of the siRNA molecules used in the present application are significantly less than the 150nm or 300nm of siRNA used by Siegmund et al to elicit the same effects (see Table 1 of Siegmund). Further evidence of the effects of the claimed siRNA, is provided by the Declaration of Daniel Longley Under 37 C.F.R. 1.132, submitted herewith. Dr. Longley is an inventor of the present invention.

The results of Figures 1 and 2 of the Longley Declaration show that significant knockdown (>96%) of c-FLIP expression can be achieved using the siRNA of SEQ ID NO 1. Figure 2 shows that the siRNA of SEQ ID NO 2 is even more effective.

The skilled artisan is not provided with any suggestion of the way to modify the siRNA disclosed by Table 1 of Siegmund to improve the potency of that siRNA. In view of this, there is no motivation or guidance provided as to the way in which the siRNA of Siegmund could have been modified to increase its potency; it would not have been routine to modify the disclosed siRNA to provide siRNA with improved potency. Thus, the claimed siRNA would not have been obvious over Siegmund.

Claims 30-39, 42, 47 and 49-52 have been again rejected as being unpatentable over Hyer et al., Uslu et al., Ni et al. and Tuschl et al. Claim 31 has been cancelled. It is respectfully submitted that Examiner has misinterpreted the arguments presented in the previous response.

Uslu et al. teaches that only selected chemotherapeutic agents provide the desired effect in selected cancer cells. Additionally, it should be noted that Hyer teaches that DU145 cells can

be sensitized to CH-11-induced cell death by pre-treatment with subtoxic concentrations of Adriamycin and Etoposide. Hyer further suggests that endogenous c-FLIP levels may contribute to the Fas-resistant phenotype of these cells. If the skilled person were to consider testing the effect of CH-11 and Adriamycin/Etoposide in the presence of a c-FLIP inhibitor, that person would not have arrived at a result falling within the scope of the above-mentioned claims, as Adriamycin and Etoposide are topoisomerase II inhibitors, not topoisomerase I inhibitors. Claims 30, 42, 49 and 51, constituting the independent claims under examination, recite compositions and kits containing topoisomerase I inhibitors. Topoisomerase I inhibitors and topoisomerase II inhibitors are different compounds, act on different substrates, and act in different ways.

Thus, even if the skilled person were to consider combining Hyer et al., Uslu et al., Ni et al. and Tuschl et al., as suggested by the Examiner, the result would not be the claimed invention.

Reconsideration and withdrawal of the Section 103 rejection of claims 30, 32-39, 42, 47 and 49-52 over the combination of Hyer et al., Uslu et al., Ni et al. and Tuschl et al. is respectfully requested.

Conclusion

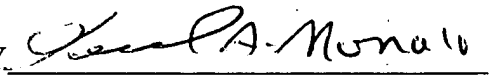
The claims remaining in the application are believed to be in condition for allowance. An early action toward that end is earnestly solicited.

Statement Under 37 C.F.R. §1.825

The sequence listing information recorded on the substitute computer readable form is identical to the written (on paper) substitute sequence listing submitted herewith. The substitute Sequence Listing includes no new matter.

Respectfully submitted,

PATRICK GERARD JOHNSTON, *et al.*

BY 

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